A General, Practical, and Versatile Strategy for Accessing ω-Functional 1,2-Diols of High Enantiomeric Excess

Thomas R. Hoye,* Michael J. Mayer, Tricia J. Vos, and Zhixiong Ye

University of Minnesota, Department of Chemistry Minneapolis, Minnesota 55455

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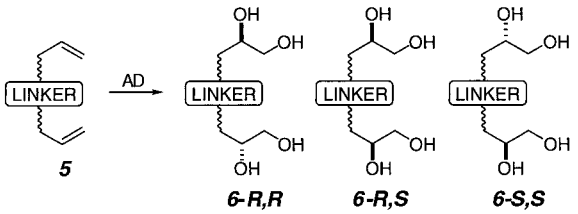
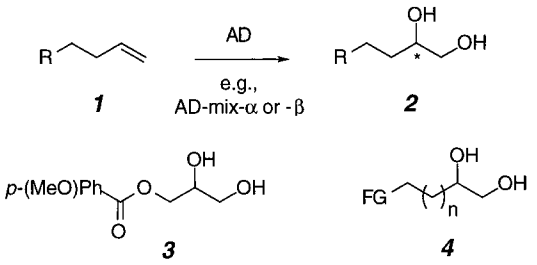
Introduction

Enantiomerically pure 1,2-diols and 1,2-epoxides are useful building blocks for synthesis. Methods for accessing these substrates include asymmetric dihydroxylation (AD) and asymmetric epoxidation (AE) of terminal alkenes, but the levels of enantiomeric excess of the derived products are often less than ideal. Considerable effort has been directed toward improving the Sharpless AD of 1-alkenes.[1] Use of the commercially available ligands $[DHQ(D)]_2$−PHAL,[2] $[DHQ(D)]_2$−PYR,[3] and $[DHQ(D)]_2$−AQN[1] provides 1,2-diols such as **2** from simple alkenes **1** with enantiomeric excesses ranging from 76 to 92%. The use of more exotic ligands does not lead to higher enantioselectivities for dihydroxylations of this class of substrate. For certain, more specialized classes of terminal alkene substrates, such as allylic and homoallylic ethers[4] and esters, the % ee's of the 1,2-diols range higher using the AD-mix-β reagent (82−95%). In the best case, allyl 4-methoxybenzoate gave a 98% ee of the glycerol derivative **3** when a (noncommercially available) pyridazine-based DHQD ligand was used.[5] Alternatively, the effect of the bulk oxidant on the enantioselectivity of the AD has been recently reported. Enantiomeric excesses of >99% were observed for the diols derived from many types of alkenes, including monosubstituted, when iodine (I_2) was used as the stoichiometric oxidant in place of the usual potassium ferricyanide in the AD-mix system.[6] We have reexamined this modification for terminal alkene substrates (see below) but have not been able to achieve improved enantiofacial selectivities [vis-à-vis the use of $K_3Fe(CN)_6$]. Finally, since 1,2-diols can be easily converted by a variety of methods into 1,2-epoxides,[7−9] it is also relevant that there are no effective methods for direct asymmetric epoxidation of alkenes such as **1** to give 1,2-epoxy analogues of **2**.[10−14,15]

Scheme 1



ω-Functional 1,2-diols (**4**) represent a subset of all 1,2-diols that are particularly versatile subunits for constructing skeletons of higher complexity. We have often had need for a variety of such building blocks and have directed attention toward developing a general and practical method for the synthesis of a family of ω-functional 1,2-diols of high enantiomeric excess. As now described, this was achieved by coupling the AD reaction with a reliable strategy for upgrading the optical purity of the product 1,2-diols.



Since many of the desired targets **4** are not likely to be crystalline, simple recrystallization of products of less than 100% optical purity[16] does not constitute a general solution for obtaining **4** with high enantiomeric excess. Thus, we looked for an appropriate derivatizing/protecting group for the terminal functionality that would be expected to render the 1,2-diol products crystalline in most instances. To also capitalize on the anticipated greater efficiency of separating diastereomeric (rather than enantiomeric) impurities from the desired product,[16] we first investigated the AD of dienes such as **5**, in which a linking group would render the tetrol products **6** crystalline (see Scheme 1). Fractional crystallization should then, at least, allow for removal of the meso diastereomer (**6-*R,S***) and, at best, also enhance the enantiopurity of the **6-*R,R***/**6-*S,S*** enantiomeric pair. A related strategy for upgrading the % ee of a chiral, nonracemic sample has been demonstrated.[17,18] In each

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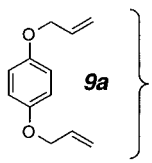
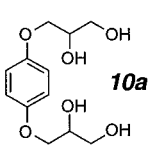
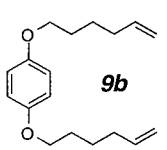
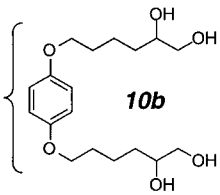
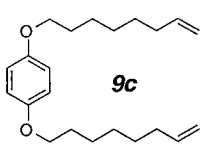
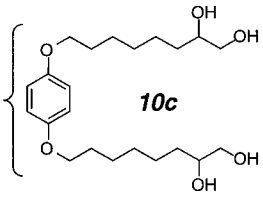
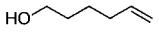
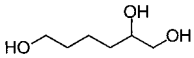
Table 1. Enantiofacial Selectivity (*R* vs *S*) in the Asymmetric Dihydroxylation of Terminal Alkene Substrates with Various AD Ligands and Different Oxidants

Alkene Substrate	$(DHQD)_2$-Ligand	Oxidant	Enantiofacial Selectivity[a] *R*:*S*	AD Product (Tetrol)
 **9a**	-PHAL	$K_3Fe(CN)_6$	1 : 15.7	 **10a**
	-PHAL	I_2	1 : 6.1	
	-PYR	$K_3Fe(CN)_6$	1 : 3.5	
	-PYR	I_2	1 : 2.6	
	-AQN	$K_3Fe(CN)_6$	1 : 49.0	
	-AQN	I_2	1 : 32.3	
 **9b**	-PHAL	$K_3Fe(CN)_6$	13.3 : 1	 **10b**
	-PHAL	I_2	8.1 : 1	
	-PYR	$K_3Fe(CN)_6$	19.0 : 1	
	-PYR	I_2	2.4 : 1	
	-AQN	$K_3Fe(CN)_6$	10.1 : 1	
	-AQN	I_2	9.0 : 1	
 **9c**	-PHAL	$K_3Fe(CN)_6$	9.0 : 1	 **10c**
	-PHAL	I_2	6.7 : 1	
	-PYR	$K_3Fe(CN)_6$	6.7 : 1	
	-PYR	I_2	4.3 : 1	
	-AQN	$K_3Fe(CN)_6$	13.3 : 1	
	-AQN	I_2	7.3 : 1	
	-PHAL	$K_3Fe(CN)_6$	3.6 : 1	
	-PHAL	I_2	3.3 : 1	
	-PYR	$K_3Fe(CN)_6$	6.7 : 1	
	-PYR	I_2	4.3 : 1	
	-AQN	$K_3Fe(CN)_6$	3.5 : 1	
	-AQN	I_2	1.8 : 1	

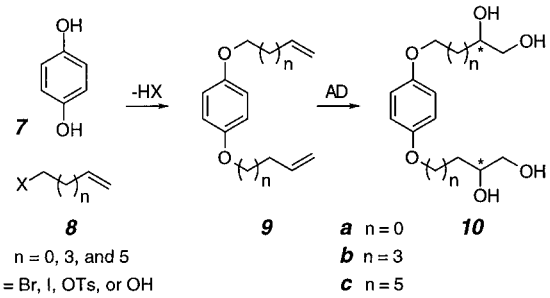
[a] Mosher ester analysis was used to determine the overall ratio of *R*- to *S*-configured stereocenters in the crude mixture of products. The ratio of *RR* : *RS* : *SS* stereoisomeric tetrols **10** equals R^2 : 2RS : S^2 under the assumption that the enantiofacial selectivity is identical for the first (on the diene) and second (on the intermediate diol alkene) AD events.[19,20]

case, a tether was used to covalently link two chiral molecules. The resulting *meso*- and *d*,*l*-diastereomers were then separated, and the starting compound, now of higher % ee, was retrieved following tether removal. The approach outlined in Scheme 1 is unique in that the linker (a) is installed prior to the establishment of the stereogenic centers and (b) can also play a subsequent beneficial role as a protecting group.

Results and Discussion

We envisioned that an ideal linker would be readily available, rigid and symmetrical (to promote crystallinity), easy to incorporate, stable to handling and a manifold of other reaction conditions, and easily and efficiently removed. Our first choice proved to be a good one. Hydroquinone (**7**) was converted to a series of alkenyl ethers **9** by alkylation with various alkenyl halides, tosylates, or alcohols (Mitsunobu) **8** (Scheme 2). Dienes **9** were then subjected to AD under various conditions. The crude mixture of tetrol products **10** for each of the 1,4-bis(2-propenyl-, 5-hexenyl-, and 7-octenyloxy)benzenes (**9a**, **9b**, and **9c**) was a solid material, and the *d*,*l*-diastereomer was crystalline in every case.

Scheme 2



Although we planned to eventually elevate the optical purity of tetrols **10**, we first surveyed various AD reaction conditions to identify those that gave the highest initial stereoselectivity. We examined the three different commercially available ligands for the Sharpless asymmetric dihydroxylation: $(DHQD)_2$−PHAL (the ligand contained in the commercial AD-mix-β reagent),[2] $(DHQD)_2$−PYR,[3] and $(DHQD)_2$−AQN.[1] Additionally, we investigated the use of iodine (I_2) as an alternative oxidant to $K_3Fe(CN)_6$.[6] The results of these studies are shown in Table 1. In every case, we used the DHQD version of the ligand (which tends to give slightly higher enantioselectivity

Table 2. Stereoisomer Enrichment through Repeated Recrystallization

compd	no. of recrystallizations	*R*:*S*[a]	yield[b] (%)
10a	0	1:49.0	93
10a	1	1:>99	68
10b	0	19.0:1	99
10b	1	24.0:1	72
10b	2	32.3:1	64
10b	3	40.8:1	51
10b	4	46.8:1	43

[a] See note *a* in Table 1. [b] Total mass recovery of all isomeric tetrols.

than the corresponding DHQ-based ligand). There is no single ligand that shows superior facial selectivity for the entire set of substrates. In our hands, the use of iodine rather than $K_3Fe(CN)_6$ never gave better stereoselectivity. For comparison, 5-hexen-1-ol was studied. The stereoselectivity of the AD of this "parent" ω-hydroxy-1-alkene was found to be lower than for the analogous **9b**, and since the product (1,2,6-hexanetriol) is a viscous oil, its optical purity could not be easily enhanced.

Each of the tetrols **10a**−**c** is crystalline. Starting with initial mixtures having total $(R/S)^{\pm 1}$ ratios (MTPA ester analysis) typically between 13:1 and 19:1, we found that recrystallization (~100 mL of EtOAc per gram of tetrol) returned material with improved total *R*/*S* ratios (Table 2). In every case, material having a ratio of >45:1 was achievable. For the simplest tetrol, the glycerol derivative **10a** derived from hydroquinone bisallyl ether **9a**,[21] a single recrystallization gave material of >99% optical purity; no minor isomers could be detected in the ^{1}H NMR spectra of the per-Mosher esters. The *R*/*S* ratio of the higher alkyl tetrols improved by several percent with each successive recrystallization, but repeated (two to five) recrystallizations were required to achieve high levels of isomeric purity. The progress of the upgrading process for **10a** and **10b** can be seen from the data in Table 2. Also, compound **10c** having an ultimate *R*/*S* ratio >45:1 could be achieved in two recrystallizations and 55% yield. For each of **10b** and **10c**, the recovered mother liquors (with an *R*/*S* ratio of approximately 13:1) could be combined and upgraded to augment the yield. Changes in solvent for the recrystallization (to ethyl acetate/ethanol or ethyl acetate/toluene) did not render the recrystallization more effective at upgrading product purity. On the basis of these results, our recommendation is to choose the ligand that gives the highest initial $(R/S)^{\pm 1}$ ratio in order to minimize the number of operations that are required to elevate the configurational purity to the desired level. This strategy represents a significant improvement over what can be achieved with simple α,ω-alkenols.

An additional advantage of this methodology is that the hydroquinone ether serves as a versatile protecting group for a primary alcohol that is compatible with many synthetic transformations. For example, in our recent synthesis of the annonaceous acetogenin (+)-parviflorin,[22] the hydroquinone moiety protected the primary alcohol during a variety of transformations (diol to epoxide; $BF_3{\cdot}OEt_2$-mediated acetylide opening of the epoxide; TBDPS protection/deprotection; Red-Al® alkyne reduction; Pd^0-catalyzed carbonylation) and was easily cleaved under mild, oxidative conditions (CAN, MeCN, H_2O, 0 °C).

In conclusion, we have developed a practical and general route to enantiomerically pure ω-functional 1,2-diols. Sharpless asymmetric dihydroxylation was used to install the desired stereogenic center(s); subsequent recrystallization was used to enhance the optical purity of the sample. This method should be both convenient and cost effective for the preparation of a wide variety of compounds belonging to this class of useful building blocks.

Experimental Section

Preparation of 1,4-bis(5-Hexenyloxy)benzene (9b) by Three Different Methods. Method A. To a suspension of potassium carbonate (3.98 g, 28.8 mmol) in DMF (60 mL) were added hydroquinone (1.05 g, 9.54 mmol) and 6-iodo-1-hexene (6.01 g, 28.6 mmol) at room temperature. The reaction mixture was warmed to 100 °C and stirred for 10 h. After being cooled to room temperature, the mixture was quenched with 10% aqueous sodium hydroxide (60 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic solutions were washed with aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified by MPLC (80:1 hexane/ethyl acetate) to give the diene **9b** (1.86 g, 71%) as a white solid: mp 29.0−30.0 °C; R_f 0.48 (9:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 4H), 5.87 (ddt, J = 16.8, 10.1, 6.7 Hz, 2H), 5.08 (ddt, J = 17.1, 1.8, 1.5 Hz, 2H), 5.02 (ddt, J = 10.1, 1.4, 0.9 Hz, 2H), 3.94 (t, J = 6.4 Hz, 4H), 2.16 (dt, J = 7.3, 7.0 Hz, 4H), 1.81 (tt, J = 6.7, 6.5 Hz, 4H), 1.61 (tt, J = 7.6, 7.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 138.6, 115.4, 114.7, 68.3, 33.6, 28.9, 25.4; IR (thin film) 3077, 1642, 1511, 1477, 1461 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.69; H, 9.37. Diene **9c** was prepared as a white solid by a similar procedure in 76% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 4H), 5.90 (ddt, J = 17.4, 10.4, 6.7 Hz, 2H), 5.14 (ddt, J = 17.1, 1.5, 1.5 Hz, 2H), 5.07 (ddt, J = 10.4, 1.5, 1.5 Hz, 2H), 3.92 (t, J = 7.0 Hz, 4H), 2.04 (dt, J = 7.3, 7.0 Hz, 4H), 1.7−1.60 (m, 4H), 1.51 (tt, J = 7.2, 7.3 Hz, 4H), 1.32 (tt, J = 7.1, 7.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 138.1, 116.1, 115.5, 76.2, 69.6, 68.6, 60.5, 33.7, 29.5, 27.0, 26.1, 25.8, 23.1, 21.2; IR (thin film) 3070, 2941, 1642, 1511, 1477, 1461 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.08; H, 10.09.

Method B. To a solution of hydroquinone (551 mg, 5.00 mmol) in THF (10 mL) were added 5-hexen-1-ol (1.67 g, 16.7 mmol) and triphenylphosphine (3.30 g, 12.6 mmol) at room temperature. Diethyl azodicarboxylate (2.21 g, 12.7 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h. The solution was decanted, and the solids were washed several times with hexanes. The organic solutions were combined and concentrated. The residue was purified by MPLC to give the diene **9b** (1.18 g, 86%).

Method C. Potassium hydroxide (1.40 g, 25.0 mmol) was dissolved in absolute ethanol (150 mL) at room temperature. To this stirred solution were added hydroquinone (0.983 g, 8.94 mmol) and 6-iodo-1-hexene (5.63 g, 26.8 mmol). The solution was heated to 80 °C and allowed to stir for 24 h. After being cooled to room temperature, the mixture was diluted with water and CH_2Cl_2, and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by MPLC to give the diene **9b** (1.89 g, 77%).

Note: To prepare other 1,4-bis(ω-alkenyloxy)benzenes, method A was preferred for the preparation of **9a** (n = 0) where a large excess of the alkenyl halide (i.e., allyl bromide) could be used. Method B was preferred for **9** (n = 1; not specifically shown) due to competing elimination reaction when 4-bromo-1-butene was used with method A. Method C was preferred when the alkenyl halide was precious (e.g., 5-iodo-1-hexene and 7-bromo- or 7-iodo-1-octene).

[*R*-(*R,*R**)]-6,6′-[1,4-Phenylenebis(oxy)]bis-1,2-hexanediol (10b). Asymmetric Dihydroxylation with $K_3Fe(CN)_6$.** To a mixture of *tert*-butyl alcohol (160 mL) and water (175 mL)

(19) Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515−524.
(20) Cf. Takahata, H.; Takahashi, S.; Kouno, S.; Momose, T. *J. Org. Chem.* **1998**, *63*, 2224−2231.
(21) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414−1418.
(22) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801−1802.

were added sequentially potassium ferricyanide (33.2 g, 100.8 mmol), potassium carbonate (13.9 g, 100.8 mmol), $(DHQD)_2$−PYR (0.285 g, 0.32 mmol), and $K_2OsO_4\cdot(H_2O)_2$ (0.023 g, 0.070 mmol) at room temperature with stirring. Once the solids had dissolved, the solution was cooled to 0 °C, and a solution of **9b** (4.76 g, 17.4 mmol) in *t*-BuOH (15 mL) was added. The slurry was vigorously stirred at 0 °C for 12 h and quenched with Na_2SO_3 (14 g). The mixture was allowed to warm to room temperature with stirring overnight and extracted with ethyl acetate (3 × 300 mL) and ethyl acetate/ethanol (4:1 v/v, 3 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude tetrol **10b** (5.7 g, 97%). The tetrol was recrystallized as described in the text (∼1 g of tetrol/100 mL of ethyl acetate): mp 105.0−105.5 °C; R_f 0.45 (4:1 ethyl acetate/ethanol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (s, 4H), 4.41 (dd, J = 5.8, 5.5 Hz, 2H), 4.08 (d, J = 5.2 Hz, 2H), 3.85 (t, J = 6.4 Hz, 4H), 3.38 (m, 2H), 3.24 (m, 4H), 1.65 (m, 4H), 1.51 (m, 4H), 1.37 (m, 2H), 1.24 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.1, 115.7, 71.5, 68.3, 66.4, 33.6, 29.5, 22.3; IR (KBr pellet) 3351, 1515, 1473, 1462 cm^{-1}; $[\alpha]^{rt}_D$ = +11.9° (c = 5.44, MeOH). Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.78. Found: C, 63.15; H, 8.83. [*R*-(*R**,*R**)]-8,8′-[1,4-Phenylenebis(oxy)]bis-1,2-octanediol (**10c**) was prepared in similar fashion in 55% yield of twice-recrystallized (EtOAc) material and 26% yield of crystalline material recovered from the mother liquors: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.82 (s, 4H), 4.47 (dd, J = 5.8, 5.5 Hz, 2H), 4.38 (d, J = 5.2 Hz, 2H), 3.87 (t, J = 6.0 Hz, 4H), 3.37 (m, 2H), 3.30−3.22 (m, 4H), 1.69−1.63 (m, 4H), 1.50−1.24 (m, 16H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 114.7, 71.1, 67.8, 66.0, 33.3, 31.3, 28.8, 25.6, 25.1; IR (KBr pellet) 3351, 1515, 1473, 1462 cm^{-1}. Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.38; H, 9.75.

Asymmetric Dihydroxylation with I_2. To a mixture of *tert*-butyl alcohol (0.4 mL) and water (0.4 mL) were added sequentially potassium carbonate (0.060 g, 0.44 mmol), iodine (0.056 g, 0.22 mmol), $(DHQD)_2$−PYR (0.002 g, 0.0015 mmol), and $K_2OsO_4\cdot(H_2O)_2$ (0.004 g, 0.03 μmol) at room temperature with stirring. Once the solids had dissolved, the solution was cooled to 0 °C, and a solution of **9b** (0.016 g, 0.058 mmol) in *t*-BuOH (0.20 mL) was added. The slurry was vigorously stirred at 0 °C for 18 h and quenched with Na_2SO_3. The mixture was allowed to warm to room temperature while being stirred and extracted with ethyl acetate (3 × 3 mL) and ethyl acetate/ethanol (4:1 v/v, 3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude tetrol (∼100%).

Tetra-Mosher Ester of Tetrol 10b. The tetrol **10b** (11 μmol, 3.7 mg) was added to a stirred solution of DMAP (11.1 μmol, 13.4 mg) and pyridine (20 μL) in CH_2Cl_2 (1 mL). (*S*)-Mosher acid chloride (MTPA-Cl, 107 μmol, 20 μL) was added, and the solution was stirred for 1 h at room temperature. Ether (5 mL) and saturated aqueous Na_2CO_3 (5 mL) were added, and the mixture was stirred for 30 min. The layers were separated, and the organic layer was washed (1 M aqueous $NaHSO_4$ and saturated aqueous NaCl), dried over magnesium sulfate, and concentrated to give the (*R*)-tetra-Mosher ester (8.1 mg, 61%) as a clear colorless oil. The product could be purified by flash chromatography (SiO_2, 2:1 hexanes/ethyl acetate) but was often sufficiently pure for direct analysis. The (*S*)-Mosher ester was also prepared by this procedure starting from (*R*)-MTPA-Cl. For in situ preparation and analysis of the Mosher ester, the tetrol (2−5 mg) was stirred in $CDCl_3$ (200 μL) with pyridine (4.8 equiv), the appropriate MTPA-Cl (4.4 equiv), and DMAP. After 24−48 h at room temperature, the solution was diluted with 500 μL of $CDCl_3$ and the ^{1}H NMR spectrum recorded.

(*R*)-Mosher ester from [*R*-(*R,*R**)]-10b.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.26 (m, 20H), 6.77 (s, 4H), 5.36 (dddd, J = 7.0, 7.0, 7.0, 3.0 Hz, 2H), 4.65 (dd, J = 12.3, 3.0 Hz, 2H), 4.33 (dd, J = 12.3, 7.0 Hz, 2H), 3.79 (dd, J = 6.0, 6.0 Hz, 4H), 3.48 (s, 6H), 3.41 (s, 6H), 1.75−1.26 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.85, −72.09.

(*S*)-Mosher ester from [*R*-(*R,*R**)]-10b.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.26 (m, 20H), 6.77 (s, 4H), 5.36 (dddd, J = 7.0, 7.0, 7.0, 3.0 Hz, 2H), 4.57 (dd, J = 12.3, 3.0 Hz, 2H), 4.29 (dd, J = 12.3, 7.0 Hz, 2H), 3.85 (dd, J = 6.0, 6.0 Hz, 4H), 3.48 (s, 6H), 3.41 (s, 6H), 1.75−1.26 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.85, −72.06.

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